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TITLE: LONGTERM FOLLOW-UP OF PATIENTS IN CSP #298 "TREATMENT OF PATIENTS WITH 'ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS) AND AIDS RELATED COMPLEX'"

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13. ABSTRACT *(Maximum 200 words)*

To evaluate the benefits of early (E) vs. Later (L) ZDV therapy, we enrolled 338 symptomatic HIV+ patients with CD4 counts of 200-500/cmm into a randomized, double-blind trial. Patients were assigned to initial ZDV 1,500 mg/day (E: 168 pts) or initial placebo (L: 170 pts). The latter were switched to ZDV after progression to AIDS or to a CD4 count <200/cmm. All pts were offered ZDV 500 mg/day following completion of blinded follow-up. Blinded and final follow-up were completed in January 1991 and 1994, respectively. Median follow-up was 52 months. Progressions to AIDS occurred in 67 and 84 pts in the E and L therapy groups, respectively (rel. risk, 0.73; 95% CI, 0.52-1.01; $p = 0.054$). Death occurred in 74 and 73 pts in the E and L therapy groups, respectively (rel. risk, 0.99; 95% CI, 0.72-1.37; *ns*). We conclude that early compared with later ZDV provides marginal protection against progression to AIDS but no survival benefit.

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I. INTRODUCTION

The Agency for Health Care Policy and Research, a division of the U.S. Public Health Service, recommends zidovudine as the first anti-retroviral treatment for patients who have CD4+ counts less than 500/mm^3, with or without symptoms (1). This recommendation is based on randomized, placebo-controlled studies that showed zidovudine to be effective in preventing progression to AIDS in this group of patients (2-4) and on retrospective cohort analyses that showed longer survival in patients who received zidovudine early in their course of illness (5,6). Nevertheless, there are conflicting data. Concorde, the largest trial published to date comparing early to delayed zidovudine therapy, showed no benefit to early therapy (7).

In 1987, the Cooperative Studies Program (CSP) of the Department of Veterans Affairs initiated a randomized trial comparing early with later zidovudine therapy in symptomatic HIV-infected patients. Double-blinded follow-up of the original cohort of 338 patients was terminated in January 1991, and the results of that portion of the study were published (8). At completion of the double-blinded follow-up, study subjects were offered continued "unblinded" zidovudine treatment in a dose of 500 mg/day at participating medical centers, and they were followed for an additional 3 years until January 1994. The results of the combined follow-up of the cohorts originally randomized to early or later zidovudine are detailed in this report.

II. METHODS

Patient population. This report combines the results of Part I and Part II of the

study; Part I (the blinded postion) was from January 1987 to January 1991, and Part II (the unblinded postion) was from January 1991 to January 1994. The criteria for selection of the original group of 338 patients were described previously (8).

The protocol and consent forms for both Part I and Part II of this study were approved by the Human Rights Committee of the Cooperative Studies Program and by the Investigational Review Board at each participating hospital. All patients gave written, informed consent.

Treatment regimens. The treatment regimens were as follows:

Early zidovudine: zidovudine treatment beginning at randomization in a dose of 1,500 mg/day in divided doses;

Later zidovudine: initial placebo changed to zidovudine when the CD4+ count fell to $<200/mm^3$ or an AIDS-defining event occurred.

Randomization of patients was completed in January 1990, and blinded follow-up was completed in January 1991. At the completion of blinded follow-up, all patients were offered zidovudine in a dose of 500 mg/day in divided doses. Thus, patients randomly assigned to later zidovudine treatment received placebo until they reached a clinical or immunological end point, defined below, or for a minimum period of 1 year.

Criteria for response. Death and AIDS were the clinical end points of this study. We used the 1987 Centers for Disease Control and Prevention (CDC) surveillance criteria for the diagnosis of AIDS throughout this study (9). Our definition of dementia was described previously (8). *AIDS-related death* was defined as death associated with a

current AIDS-defining condition. *Death with HIV progression* was defined as death preceded by AIDS or an HIV-associated illness (e.g., pneumococcal bacteremia and meningitis), increased symptoms, or a fall in CD4+ concentration to <200 cells per cubic millimeter. The immunological end point of this study was the fall in CD4+ concentration to less than 200 cells per cubic millimeter on two successive measurements done 6 or more weeks apart.

Evaluation and follow-up. Follow-up of patients was at least monthly during Part I and at least bimonthly during Part II of this study. A detailed history, physical examination, and laboratory studies were obtained at each of these evaluations.

Data management and statistical analyses. Data collected at participating sites were sent to the study co-chairman's office and the CSP Coordinating Center for review. Methods of data verification and entry were described previously (8). Comparability of treatment groups was assessed by a chi-square test or Fisher's exact test for discrete variables, or by Student's *t* test or Wilcoxon rank-sum test for continuous variables (10). Time to clinical and immunologic end points was estimated with Kaplan-Meier and proportional-hazards regression methods. Stratified log-rank tests and proportional hazards models were used to compare treatment groups and to estimate relative risks and confidence intervals (CIs), adjusting for the stratification by CD4+ cell concentration (11). Qualitative interactions were tested with the method developed by Gail and Simon (12). Throughout, we have reported the relative risks comparing early with later zidovudine treatment.

III. RESULTS

Patient characteristics. The baseline characteristics of our original cohort of 338 patients were described in our earlier manuscript (8). Forty-four (44) patients died, and 15 patients were lost to follow-up during Part I of this study. There were 9 other patients from whom no data were collected during Part II. Thus, Part II had 270 patients, equally divided between the two treatment groups, from whom data were collected. Table 1 summarizes the baseline characteristics of the patients followed in Part II of the study. There were no differences between the treatment groups, nor were there significant differences between this group and the group that died or was lost during Part I of the study.

Progression to AIDS. CDC-defined AIDS occurred in 67 and 84 patients in the early- and later-therapy groups, respectively (Table 2). There were no significant differences in the occurrences of individual AIDS-defining diagnoses between the treatment groups. The number of patients with first AIDS events in each treatment group at yearly intervals of follow-up is shown in Table 3, Part A. The relative risk of progression to AIDS and the 95% CIs for early compared with later treatment are also shown. The relative risk for progression to AIDS ranged from 0.68 to 0.73. The 95% CIs just barely overlapped 1 at 3, 4, and 5 years of follow-up and at study conclusion. A Kaplan-Meier lifetable plot of the time to AIDS in the study population is shown in Figure 1. The median time to AIDS in the later-therapy group was 57.4 months whereas it was 68.2 months in the early-therapy group. This is a difference of almost 11 months. By stratified log-rank test, the p was 0.054.

Deaths. There were 74 deaths in the early-therapy group and 73 deaths in the later-therapy group (Table 3, Part B). The relative risk of death for the early-therapy group was close to 1 throughout the study (Figure 2A). A Kaplan-Meier lifetable analysis of the time to death showed virtually identical curves in the two treatment groups. The median times to death was 65.8 months and 68.7 months in the early- and later-therapy groups, respectively. By stratified log-rank test, the p was 0.96 (Table 4). Of the 74 patients who died in the early-therapy group, 48 (65%) had AIDS, an additional 16 (22%) had an AIDS-related disease, and 10 died of AIDS-unrelated or unknown causes. Of the 73 patients who died in the later-therapy group, 64 (87.6%) had AIDS, an additional 3 (4%) had an AIDS-related disease, and 6 (8%) died of AIDS-unrelated or unknown causes (Figure 2B). For survival after an AIDS diagnosis, there was little difference between the two therapy groups. The median survival after AIDS in the early-therapy group was 12.9 months; it was 15.9 months in the later-therapy group (p = 0.64).

Immunologic progressions. Absolute CD4+ counts increased in the early-therapy group (Figure 3). In this group, the mean absolute CD4+ remained above baseline for the first year of follow-up. In the later-therapy group, the CD4+ counts declined steadily. Statistically significant differences between the treatment groups persisted for over 3 years of follow-up.

IV. CONCLUSIONS

Our data indicate that early zidovudine therapy for patients with symptomatic

HIV infection and initial CD4+ counts between 200 and 500/mm^3 results in a significant, sustained CD4+ count elevation and provides marginal protection against progression to AIDS but no survival benefit. These findings are similar to those that we previously reported (8). However, by extending the period of follow-up for our patients, we have increased the number of events observed and narrowed the confidence intervals of our relative risk estimates.

Our findings that early zidovudine therapy reduced the risk of AIDS-defining events is similar to that reported in other prospective zidovudine-versus-placebo-controlled trials, including those reported by the AIDS Clinical Trials Group (3,4) and by the European-Australian Collaborative Group (13). It must be recognized, however, that many of the opportunistic infections observed in our study and in the others reported can be prevented by other forms of prophylaxis that are now widely used (1).

Our findings on death are similar to those reported by the Concorde Coordinating Committee (7). In the Concorde trial, as in ours, there was a trend toward an increased death rate in the early-therapy group. These findings tend to support the now more widely held view that prolonged anti-retroviral monotherapy may not be of benefit and, in some instances, may be detrimental to HIV-infected patients (14).

Despite optimistic statements, the optimum time for initiating anti-retroviral therapy remains a legitimate subject for debate among investigators (15), as well as a subject for discussion between patients and their physicians. Although there is hope that cycles or combinations of anti-retrovirals will reduce morbidity and prolong survival of HIV-infected patients, the clinical trials necessary to prove these clinical benefits have

not been completed.

V. ADDENDUM (specimens sent to Walter Reed)

Another goal of the project was to collect and send to the Army research laboratory under the direction of Dr. Douglas Mayers an aliquot of lymphocytes from each blood specimen received at the study's reference laboratory at Duke University. In addition, an aliquot of the supernatant from all positive cultures was to be forwarded to the same laboratory. During the period of the study, these specimens were regularly assembled and sent as prescribed. The final shipment is currently being assembled and will be forwarded by October 15, 1994.

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VII. BIBLIOGRAPHY

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B. Abstracts presented

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VIII. LIST OF PERSONNEL RECEIVING PAY FROM THE CONTRACT SUPPORT

A. Patient treatment centers:

Manhattan VAMC: Noreen Haren, R.N.; Eileen Bailey, R.N.

Miami VAMC: Gishlaine Paperwaller, R.N.; John Roussel, M.S. microbiology (laboratory technician)

Houston VAMC: Adonna Peacock, R.N.; Joanne Mitchell

Los Angeles VAMC: Carol Silbar, R.N.; Felicitas Lorenzo, R.N.

San Francisco VAMC: Roland Jalbert, R.N., Manon Maravich, R.N., Ann

Cotleur, B.S. (lab technician)

Washington, DC, VAMC: Patricia Ackerson, R.N.

Durham, NC, Cochairs Office: Patricia Spivey, Study Coordinator; Clorine Chasten, Isabel Routh, Lucy Skinner, secretaries

Duke Virology Laboratory, Durham, NC: Debbie Wakefield (laboratory technician), Janet Ottinger (laboratory technician), Caroline Hinton (laboratory technician),Tom Matthews, Ph.D. (laboratory supervisor)

Baltimore VAMC Reference Laboratory: Mark Rossen (laboratory technician)

Table 1

Baseline Characteristics of Patients Followed in Part II

	Zidovudine Treatment	
	Early (N=135)	Later (N=135)
Stratum - No. (%) of patients		
1	33 (24)	34 (25)
2	102 (76)	101 (75)
Age at randomization (yr)	40.4	40.2
Sex - No. of patients		
Male	133	134
Female	2	1
Race - No. (%) of patients		
Non-Hispanic white	92 (68)	94 (69)
Black or Hispanic	37 (27)	39 (29)
Risk group - No. (%) of patients		
Homosexual or bisexual	87 (65)	82 (61)
Intravenous drug use	20 (15)	26 (19)
Homosexual and IVDU	14 (10)	13 (10)
Other	14 (10)	14 (10)
No. of symptoms (Mean)	3.0	3.3
CD4+ count/mm^3 - Mean$\pm$SD	353.4$\pm$92.7	362$\pm$80.7
Karnofsky score	8.9	8.9

Table 2

Progression to AIDS - First Diagnoses

	Zidovudine Treatment	
Diagnosis	Early	Late
Kaposi's sarcoma	8	12
PCP	21	25
Esophageal candidiasis	16	10
Disseminated MAC infection	4	4
Toxoplasmosis	2	3
Cryptococcosis	1	1
Cryptosporidiosis	0	1
PML	1	4
Lymphoma	2	7
CMV (retinitis or GI)	4	7
Disseminated herpes	1	1
Extra-pulmonary TB	1	0
Dementia	2	7
Wasting	4	2
Total	67	84

Table 3

Number of Patients and Relative Risk of Progression to AIDS and Death

A. Progression to AIDS

	Zidovudine Treatment			
Follow-up	Early	Late	Relative risk (95% CI)	*p*
1 Year	11	15	0.69 (0.32 - 1.52)	
2 Years	25	35	0.68 (0.95 - 1.13)	
3 Years	40	55	0.69 (0.46 - 1.09)	
4 Years	54	71	0.71 (0.50 - 1.00)	
5 Years	54	78	0.73 (0.52 - 1.02)	
Final	67	84	0.73 (0.52 - 1.01)	0.054

B. Death

	Zidovudine Treatment			
Follow-up	Early	Late	Relative risk (95% CI)	*p*
1 Year	5	3	1.62 (0.39 - 6.72)	
2 Years	11	8	1.35 (0.54 - 3.36)	
3 Years	34	22	1.51 (0.88 - 2.59)	
4 Years	50	51	0.97 (0.65 - 1.44)	
5 Years	68	63	1.06 (0.74 - 1.50)	
Final	74	73	0.99 (0.72 - 1.37)	0.962

Table 4

Relation Between AIDS, HIV-Related Disease, and Death

	Zidovudine Treatment	
	Early	Later
Prior AIDS	48 (64.9%)	64 (87.7%)
HIV-related disease	16 (21.6%)	3 (4.1%)
Unrelated or unknown	10 (13.5%)	6 (8.2%)
Total	74 (100%)	73 (100%)

LEGENDS

Figure 1. Estimated Kaplan-Meier distribution of the time to AIDS, according to study group.

Figure 2A. Estimated Kaplan-Meier distribution of the time to death, according to study group.

Figure 2B. Estimated Kaplan-Meier distribution of the time from an AIDS diagnosis to death, according to study group.

Figure 3. Mean ($\pm$SE) changes from baseline in absolute CD4+ counts, according to study group.

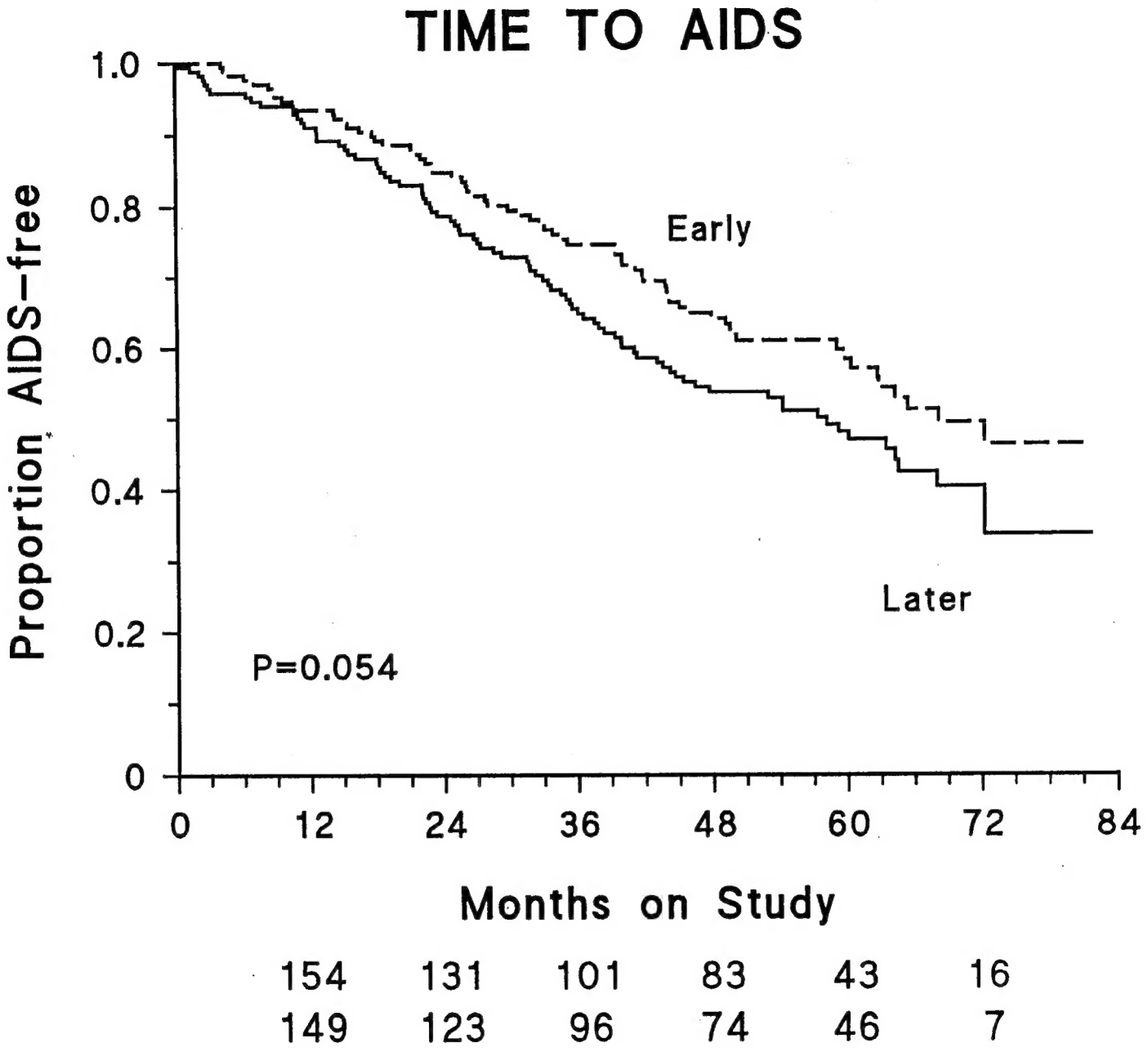
TIME TO AIDS
Proportion AIDS-free
1.0
0.8
0.6
0.4
0.2
0
Early
Later
P=0.054
0
12
24
36
48
60
72
84
Months on Study
154 131 101 83 43 16
149 123 96 74 46 7

Figure #1

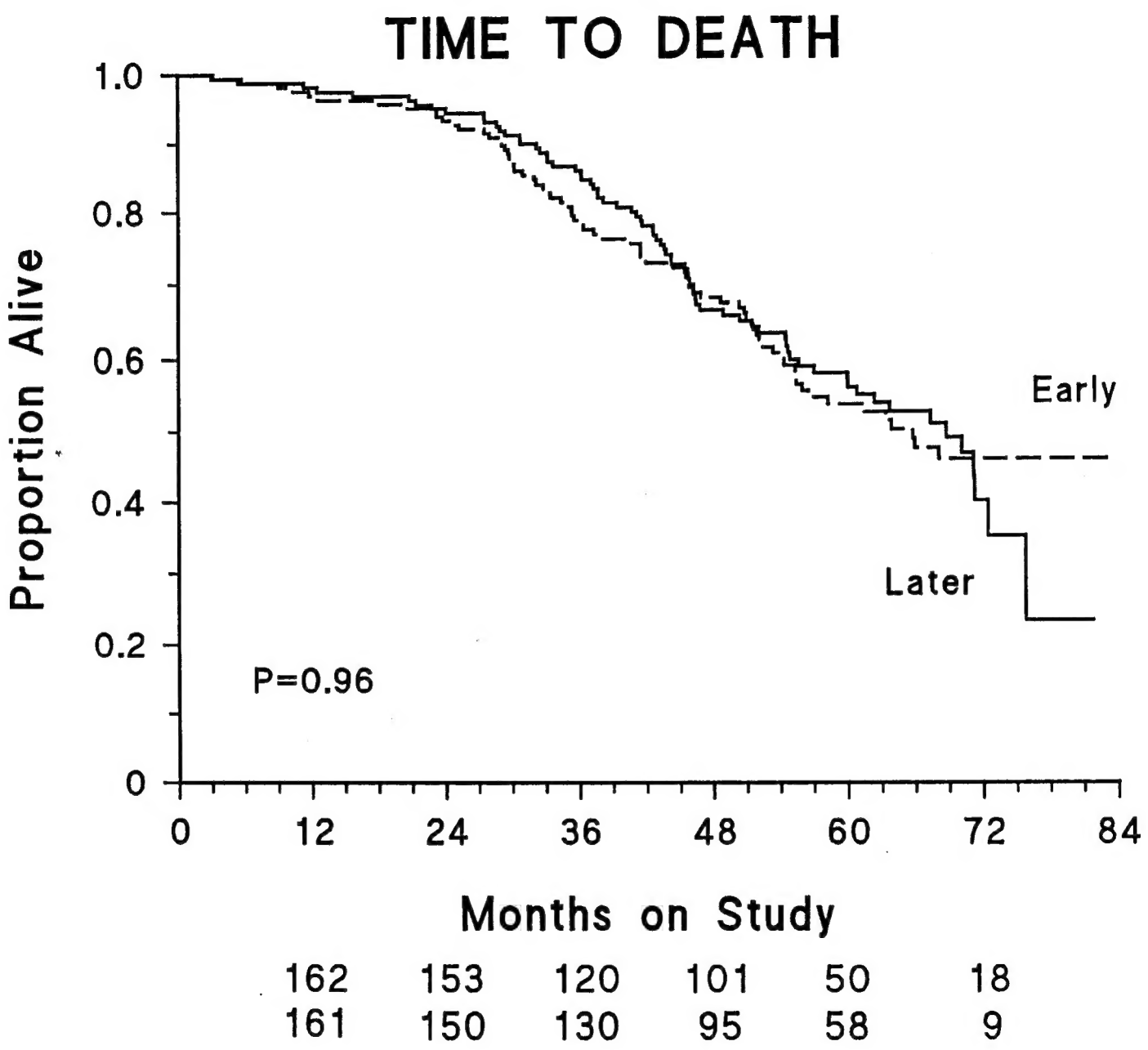
TIME TO DEATH
Proportion Alive
1.0
0.8
0.6
0.4
0.2
0
Early
Later
P=0.96
0
12
24
36
48
60
72
84
Months on Study
162 153 120 101 50 18
161 150 130 95 58 9

Figure 2A

SURVIVAL AFTER AN AIDS DIAGNOSIS

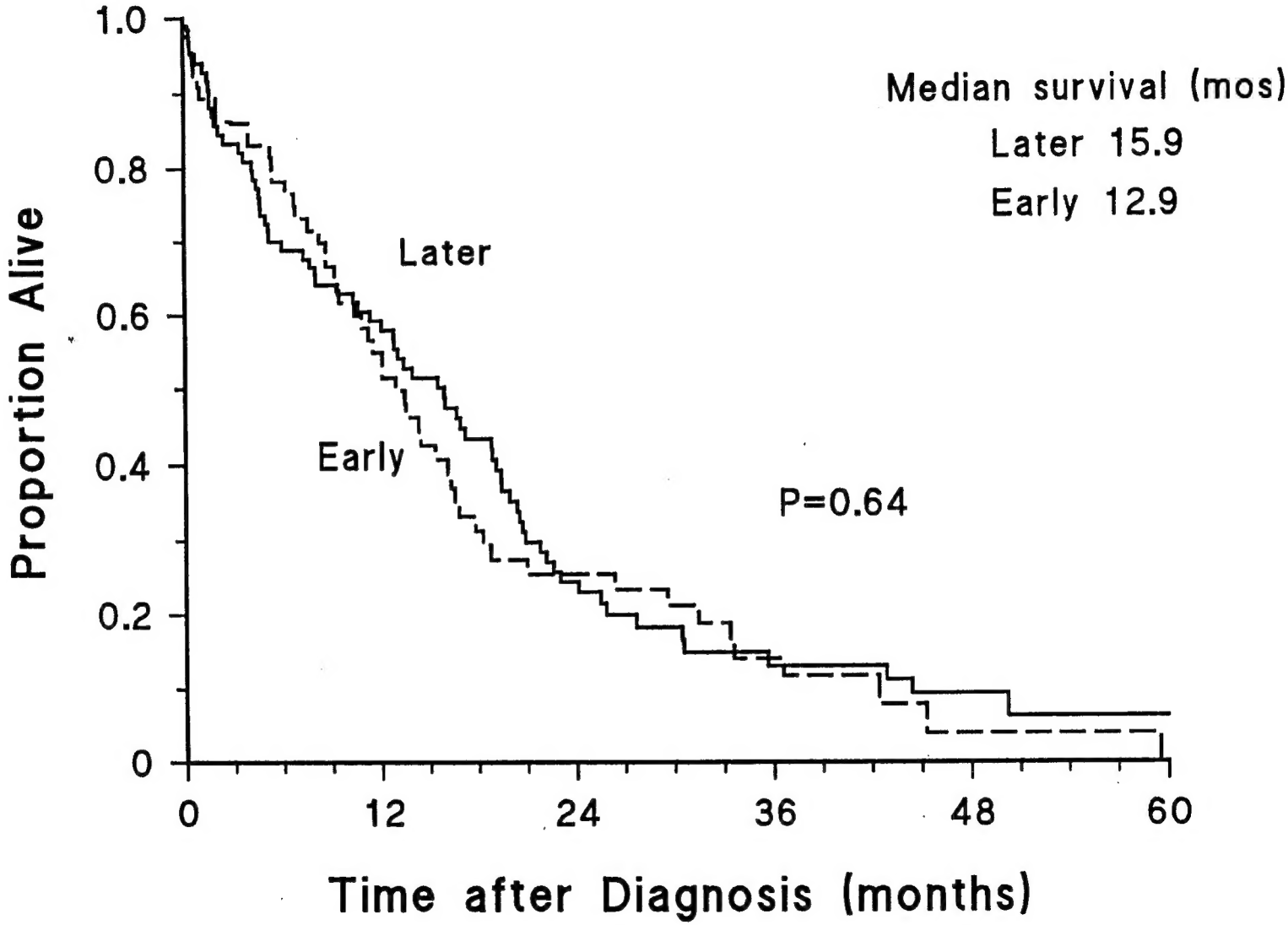

Figure 2B

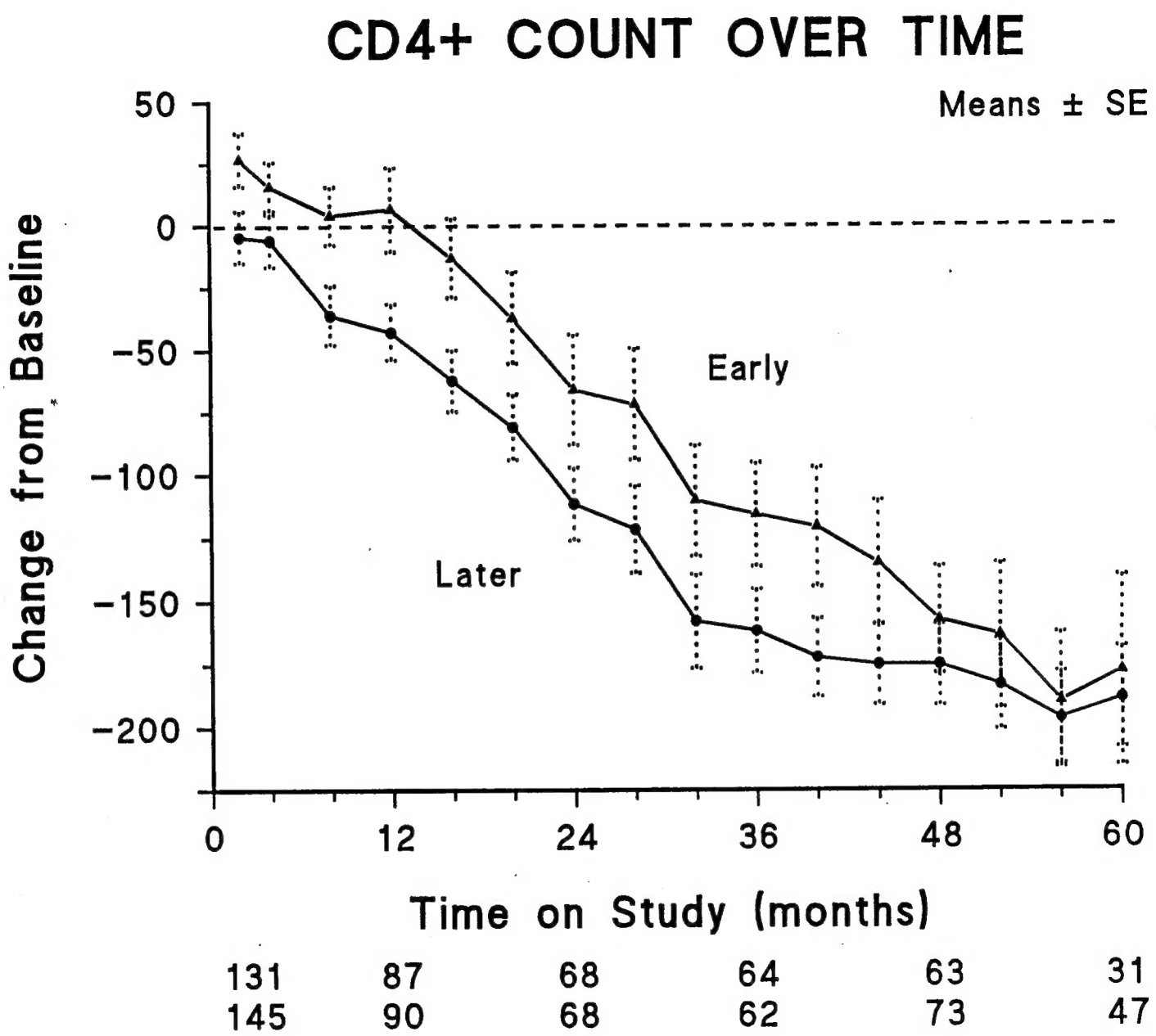
CD4+ COUNT OVER TIME
Means ± SE
Change from Baseline
50
0
−50
−100
−150
−200
Early
Later
0
12
24
36
48
60
Time on Study (months)
131 87 68 64 63 31
145 90 68 62 73 47

Figure 3